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EXAMINER	
BUNNER, BRIDGET E	

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1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,292	KRAUSE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-19 and 21-25* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☒ Claim(s) *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 03 June 2009 has been entered in full. Claims 13, 15-19, 21-23 are amended. Claims 24-25 are added.

Claims 1-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 December 2008.

Claims 13-25 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claims 16 and 21-23 at page 3 of the previous Office Action of 03 March 2009 is *withdrawn* in view of the amended claims (03 June 2009).

2. The rejection of claims 13-23 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (03 March 2009) is *withdrawn* in view of the amended claims (03 June 2009).

3. The rejection of claims 13 and 14 under 35 U.S.C. § 102(b) as set forth at pages 4-5 of the previous Office Action (03 March 2009) is *withdrawn* in view of the amended claims (03 June 2009). Specifically, Okada et al. do not teach an antibody concentration between about 20 and about 130 mg/ml as required by the amended claims. Okada et al. only disclose a concentration from 0.01 mg/ml to 10 mg/ml.

4. The rejection of claims 15, 17, 18, and 19 under 35 U.S.C. § 103(a) as being unpatentable over Okada et al. as set forth at pages 6-7 of the previous Office Action (03 March 2009) is *withdrawn* in view of the amended claims (03 June 2009).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Gombotz et al. (US 20030180287). The basis for this rejection is set forth at pages 4-5 of the previous Office Action (03 March 2009).

Applicant's arguments (03 June 2009), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 6 of the Response, Applicant argues that Gombotz et al. discloses and claims Fc domain containing polypeptide formulations that contain either L-arginine or L-cysteine. Applicant asserts that the Fc containing polypeptides are Fc domain fusion proteins, such as a soluble form of the TNF receptor fused to an Fc domain. Applicant indicates that Gombotz et al. mentions the use of antibodies in his L-arginine or L-cysteine formulations but provides no guidance data on the suitability of such formulations. Applicant points out that the instant claims

do not recite compositions or formulations containing either L-arginine or L-cysteine, nor Fc domain fusion proteins.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Gombotz et al. teach an aqueous pharmaceutical composition comprising an antibody or an Fc domain containing polypeptide, a buffer, tonicity modifier, and one or more excipients (page 1, [0006]; page 3, [0035-0036]; pages 4-5, [0052]). Gombotz et al. teach that the formulations and methods of the invention can be used to prepare pharmaceutical compositions comprising antibodies, thus meeting the limitations of the instant claims (page 3, [0034]). Gombotz et al. add that examples of antibodies for use in the invention include those that recognize tumor necrosis factor alpha (TNF-α) (page 3, [0036]). Gombotz et al. disclose a range of dosages for Fc domain containing polypeptides and state that "the formulation will depend on the condition to be treated, the severity of the condition, prior therapy, and the patient's clinical history and response to the therapeutic agent (page 4, [0051]; page 5, [0057-0058]). It is clear from the disclosure of Gombotz et al. that antibody formulations would also have these dosage ranges since antibodies are technically Fc domain containing polypeptides. The Examiner acknowledges that Gombotz et al. includes L-arginine or L-cysteine in the antibody formulations. However, the instant claims recite “comprising” language and have been interpreted by the Examiner as open terminology. Thus, the term “comprising” still allows for the inclusion of other elements in the claimed pharmaceutical composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 15, 17, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al. (EP 1174148; 4/27/2000) and Gombotz et al. (US 20030180287) as applied to claims 13 and 14 above. The basis for this rejection is set forth pages 6-7 of the previous Office Action (03 March 2009).

Applicant's arguments (03 June 2009), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 7 of the Response, Applicant argues that a person of ordinary skill in the art would not have a reasonable expectation of success and that such formulations are not routine. Applicant contends that Gombotz et al. fails to teach or suggest the specific amounts and

combinations of ingredients, either alone or in combination, which formulations Applicant has demonstrated through a working example in the instant specification results in a pharmaceutical formulation with both improved shelf life and the ability to dissolve high concentrations of proteins. Applicant asserts that the claimed formulations are inventive in that they embody Applicant's discovery that the claimed formulations are effective in improving the stability of an antibody at high antibody concentration in the liquid state.

Applicant's arguments have been fully considered but are not found to be persuasive. Gombotz et al. teach a composition comprising a buffer that maintains the composition pH at a range of about 6.0 and about 7.0 (page 1, [0006]; page 4, [0046]). Gombotz et al. teach that buffering agents include potassium phosphate and sodium or potassium citrate and that the concentration of the buffer is between about 1mM to about 1M (page 4, [0045]). Gombotz et al. disclose that a tonicity modifier includes mannitol (page 4, top of column 2, [0047]). Gombotz et al. teach that the concentration of the tonicity modifier is between about 1 mM to 1M (page 4, top of column 2, [0045]). Additionally, Gombotz et al. indicate that a suitable excipient to stabilize the polypeptide while in solution includes Tween-80 (also known in the art as polysorbate 80) (page 4, [0048]). Gombotz et al. indicate the concentration of the excipient is between about 0.001 to 5 percent weight percent (page 4, [0049]). Gombotz et al. teach that the formulation can comprise about 10 to about 100 mg/ml of the polypeptide (page 4, [0051]; page 5, [0058]).

Although Applicant argues that the claimed formulations are an unexpected discovery in improving the stability of an antibody at high antibody concentration in the liquid state, Gombotz et al. specifically states that the invention provides "a novel stable liquid formulation that allows

long term storage of a polypeptide containing an Fc domain of an immunoglobulin" (page 1, [0005], [0023]). Gombotz et al. also teaches that the formulation is useful because it is more convenient to use for the patient, as this formulation does not require any extra steps such as rehydrating (page 1, [0023]). In view of Gombotz et al.'s statement above and the teaching of overlapping concentration ranges of the recited ingredients, it is clear that the claimed ranges do not achieve unexpected results relative to the ranges disclosed in Gombotz et al.

As discussed in the previous Office Action, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the amounts of buffer, disaccharide/tonicity modifier (i.e., mannitol), and surface agent/excipient (i.e., Tween-80) utilized in the compositions as taught by Gombotz et al. The person of ordinary skill in the art would have been motivated to make that modification to in order to improve upon what is already known, thus determining the optimum combination amounts of reagents. The person of ordinary skill in the art reasonably would have expected success because optimization of conditions is routine in the art. See *In re Aller* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation". See also *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.).

Furthermore, to establish unexpected results over a claimed range, Applicant should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range (see *In re Hill*, 284 F.2d 955, 128 USPQ 197 (CCPA 1960).

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gombotz et al. (US 20030180287) as applied to claims 13-14 above, and further in view of Salfeld et al. (U.S. Patent 6,090,382). The basis for this rejection is set forth at pages 7-8 of the previous Office Action (03 March 2009).

8. Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gombotz et al. (US 20030180287) as applied to claims 15, 17, 18, and 19 above, and further in view of Salfeld et al. (U.S. Patent 6,090,382). The basis for this rejection is set forth for claims 21-23 at pages 8-9 of the previous Office Action (03 March 2009).

Applicant's arguments (03 June 2009), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 8 of the Response, Applicant argues that Salfeld et al. does not cure the deficiencies of Gombotz et al. Applicant states that Salfeld et al. fails to teach or suggest a composition comprising the concentrations of the specific ingredients required by the claims. Applicant asserts that the working example in the instant application results in a pharmaceutical composition with improved shelf life and the ability to dissolve high concentrations of proteins. Applicant contends that it would not have been obvious to one of skill in the art to combine the specific ingredients of the claims to arrive at the pharmaceutical formulation with improved stability and/or a high protein concentration. Applicant asserts that the claimed formulations are

inventive in that they embody Applicant's discovery that the claimed formulations are effective in improving the stability of an antibody at high antibody concentration in the liquid state.

Applicant's arguments have been fully considered but are not found to be persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As discussed above, although Applicant argues that the claimed formulations are an unexpected discovery in improving the stability of an antibody at high antibody concentration in the liquid state, Gombotz et al. specifically states that the invention provides "a novel stable liquid formulation that allows long term storage of a polypeptide containing an Fc domain of an immunoglobulin" (page 1, [0005], [0023]). Gombotz et al. also teaches that the formulation is useful because it is more convenient to use for the patient, as this formulation does not require any extra steps such as rehydrating (page 1, [0023]). In view of Gombotz et al.'s statement above and the teaching of overlapping concentration ranges of the recited ingredients, it is clear that the claimed ranges do not achieve unexpected results relative to the ranges disclosed in Gombotz et al.

Additionally, Gombotz et al. teaches a formulation comprising an anti-TNFα antibody. However, Gombotz et al. does not disclose the anti-TNFα antibody, D2E7. Salfred et al. was cited by the Examiner because Salfred et al. teach the specific recombinant anti-hTNFα antibody, D2E7. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the aqueous pharmaceutical composition as taught by Gombotz et al. by substituting the antibody or an Fc domain containing polypeptide with the anti-hTNFα

antibody, D2E7, as taught by Salfeld et al. The person of ordinary skill in the art would have been motivated to make that modification to provide a stable liquid formulation that allows long term storage of the antibody (see for example, Gombotz et al., page 1, [0005], [0023]). The person of ordinary skill in the art reasonably would have expected success because similar preparations were already being generated at the time the invention was made.

New Claim Objections/Rejections

Claim Objections

9. Claims 20, 24 and 25 are objected to because of the following informalities:

9a. In claim 24, line 24, the term "polysorbate 80" is underlined. The underline should be removed.

9b. In claim 25, line 2, the recitation of "mg/mL" should be amended to recite "mg/ml" in order to be consistent with the other pending claims.

9c. Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

10. Claims 17 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 17 is directed to a liquid aqueous pharmaceutical formulation comprising (a) about 2 to about 150 mg/ml of antibody, (b) about 5 to about 20 mg/ml of mannitol, (c) about 0 to about 15 mg/ml of polysorbate 80, and (d) a buffer system comprising at least one buffer. Claim 25 is directed to a stable pharmaceutical formulation comprising Adalimumab at a concentration of between about 2 and about 150 mg/mL, wherein said formulation has a pH of about 4 to about 8.

(i) The specification as originally filed does not provide adequate written description for "about 0 to about 15 mg/ml of polysorbate 80". At page 18 of the specification, the Examiner was only able to find support for "between about 0.1 and about 10 mg/ml of polysorbate 80" and "between about 0.5 and about 5 mg/ml" (see lines 30-33).

(ii) The specification as originally filed does not provide adequate written description for "Adalimumab". It is not expressly asserted, nor does it flow naturally from the specification.

Claim Rejections - 35 USC § 103

11. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gombotz et al. (US 20030180287) and Salfeld et al. (U.S. Patent 6,090,382).

Gombotz et al. teach an aqueous pharmaceutical composition comprising an antibody or an Fc domain containing polypeptide, a buffer, tonicity modifier, and one or more excipients (page 1, [0006]; page 3, [0035-0036]; pages 4-5, [0052]). Gombotz et al. teach that the formulations and methods of the invention can be used to prepare pharmaceutical compositions

comprising antibodies (page 3, [0034]). Gombotz et al. add that examples of antibodies for use in the invention include those that recognize tumor necrosis factor alpha (TNF-α) (page 3, [0036]). Gombotz et al. disclose that the buffer maintains the composition pH at a range of about 6.0 and about 7.0 (page 1, [0006]; page 4, [0046]). Gombotz et al. teach that the formulation can comprise about 10 to about 100 mg/ml of the Fc domain containing polypeptide (page 4, [0051]; page 5, [0058]).

Gombotz et al. does not disclose an aqueous pharmaceutical composition comprising the antibody, Adalimumab.

Salfeld et al. teaches TNFα is implicated in the pathophysiology of a variety of human diseases, such as shock, sepsis, infections, autoimmune diseases, transplant rejection and graft-versus-host disease (column 1, lines 10-20). Salfeld discloses that therapeutic strategies have been designed to inhibit or counteract hTNFα activity, in particular antibodies that bind to and neutralize hTNFα (column 1, lines 23-27). Salfeld et al. teach a recombinant anti-hTNFα antibody, termed D2E7, neutralizes hTNFα activity (column 2, lines 50-67; column 9, lines 43-67 through column 5). It is well known in the prior art that the antibody D2E7 is also known as adalimumab (see entry for "adalimumab" from the National Library of Medicine; www.nlm.nih.gov/cgi/mesh). Salfeld et al. disclose administering an anti-hTNFα to a human subject suffering from a disorder in which TNFα activity is detrimental such that human TNFα activity in the human subject is inhibited (column 4, lines 32-48; columns 24-27). Salfred et al. teach the antibody can be incorporated into pharmaceutical compositions suitable for administration (column 20, lines 59-61). Salfred et al. state that examples of pharmaceutically

acceptable carriers include phosphate buffered saline, glycerol, ethanol, among others (column 21, lines 1-21).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the aqueous pharmaceutical composition as taught by Gombotz et al. by substituting a TNF-α antibody with the specific anti-hTNFα antibody, D2E7 (adalimumab), as taught by Salfeld et al. The person of ordinary skill in the art would have been motivated to make that modification to provide a stable liquid formulation that allows long term storage of the antibody (see for example, Gombotz et al., page 1, [0005], [0023]). The person of ordinary skill in the art reasonably would have expected success because similar preparations were already being generated at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
28 September 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647